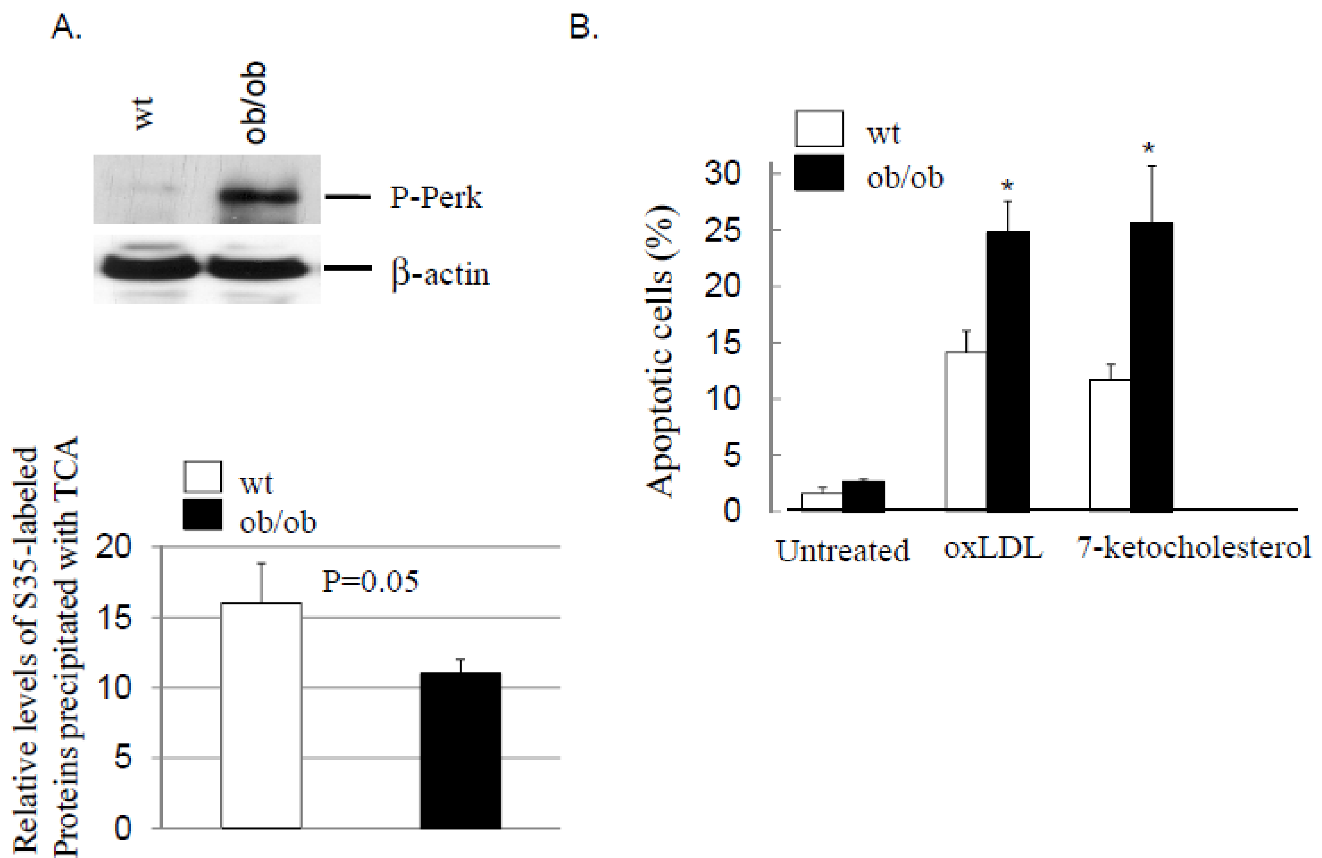
SUPPLEMENTARY DATA

Supplementary Figure 1. **(A)** (Top) Fresh peritoneal macrophages from either ob/ob or lean wild-type (wt) mice fed regular chow diet were cultured at 37°C in DMEM with 10% FBS for 2 hr. Cells were harvested and protein extracts were prepared. Western analysis was performed with antibodies against the proteins as indicated. n=3. (Bottom) Pulse-labeling of cells from wt and ob/ob mice with 35S-methionine was performed. The amounts of 35S label incorporation by trichloroacetic acid (TCA) precipitation were then measured. The results were normalized to total cell counts. **(B)** Pooled ConA-elicited peritoneal macrophages were incubated with or without oxLDL (100 µg/ml) or 7-ketocholesterol (40 ug/ml) at 37°C for 8 h. Apoptosis of macrophages was determined by annexin V staining. All results represent average ± SE. *, P<0.05 for oxLDL or 7-ketocholesterol-loaded wt vs. ob/ob cells. n=3. **(C)** ConA-elicited peritoneal macrophages isolated from ob/ob and wt mice were treated as described in Fig 1A. The levels of indicated mRNAs regulated by PERK/ATF4, ATF6, and IRE1/XBP1 arms of the UPR were measured by real time QPCR. n=3.



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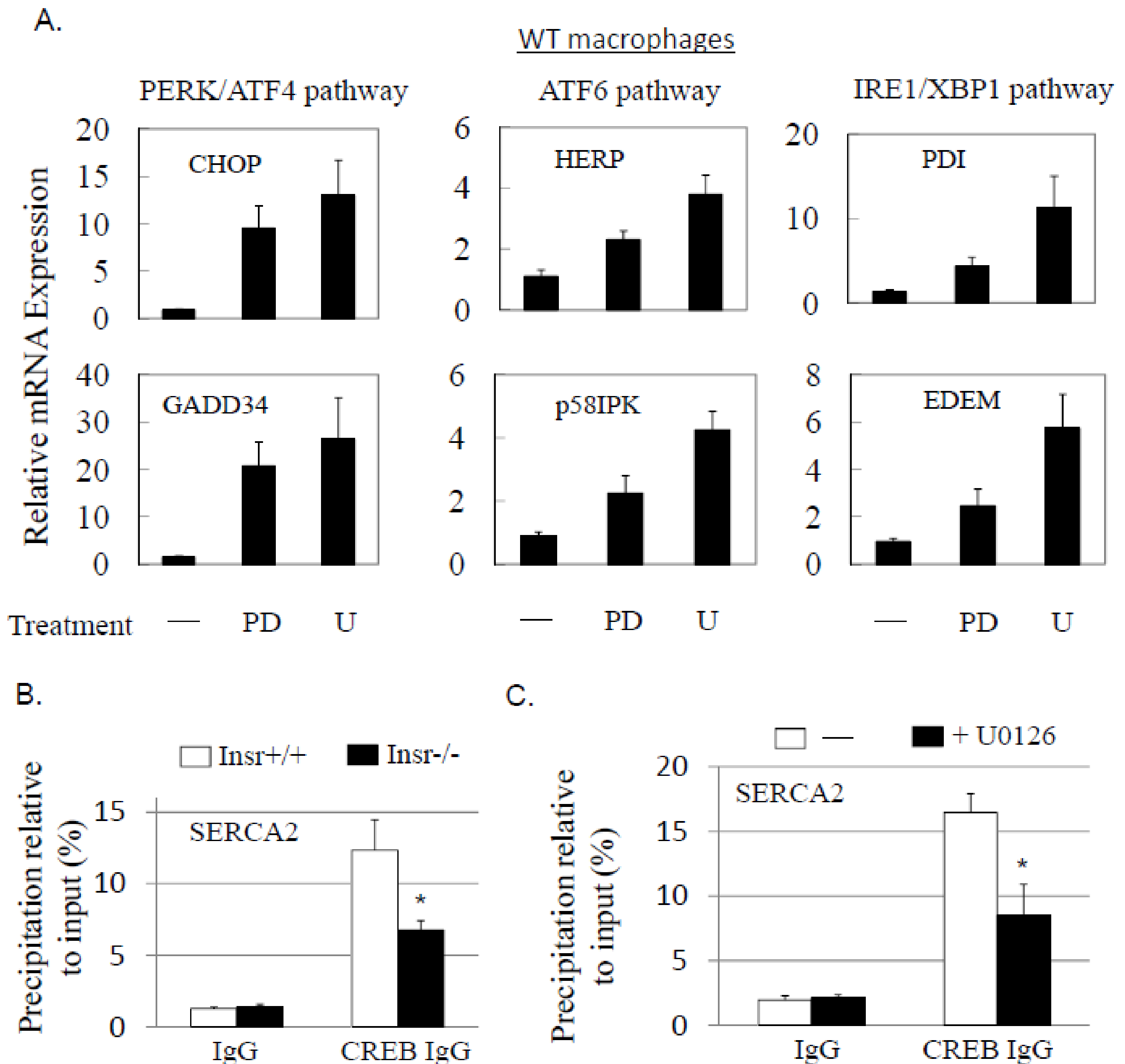
Supplementary Figure 2. (A) The mRNA expression of macrophage PERK/ATF4, ATF6, and IRE1/XBP1 target genes was measured by real time QPCR as described in Fig 1A. QPCR was performed in triplicate. n=3. **(B)** Chromatin immunoprecipitation (ChIP) analysis of the association of P-CREB to SERCA2 gene promoter in Insr+/+ and Insr-/- macrophages. Cells were cultured as described in (A), and ChIP analysis was performed with a ChIP assay kit. ChIP samples were quantified by real-time qPCR and results were presented as percent precipitation relative to input chromatin. n=4. *,P<0.05. **(C)** ChIP analysis of the association of P-CREB to SERCA2 gene promoter in wild-type macrophages with or without 4h-treatment of MEK inhibitor U0126 (10 uM). ChIP analysis was performed with a ChIP assay kit. ChIP samples were quantified by real-time qPCR and results were presented as percent precipitation relative to input chromatin. n=3. *,P<0.05.



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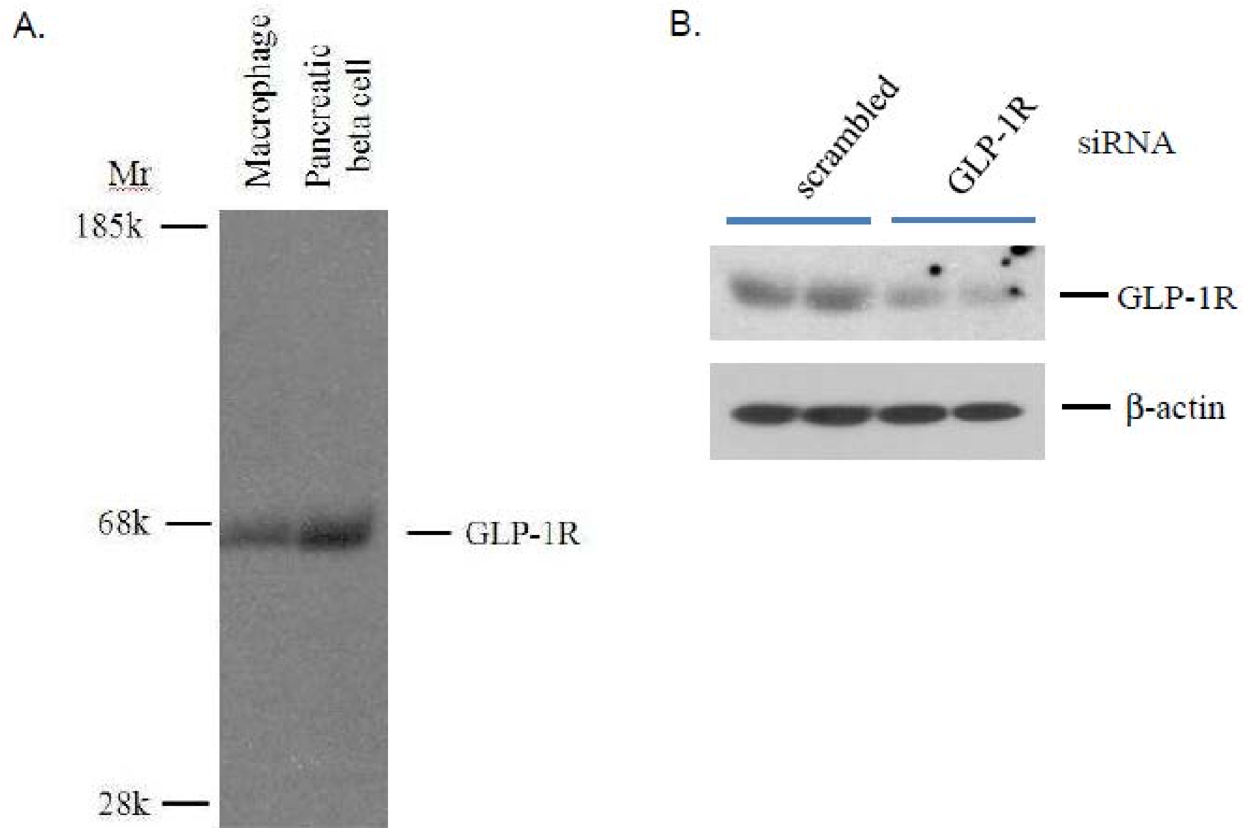
Supplementary Figure 3. (A) The expression of GLP-1 receptor in primary macrophages from wild-type mice as well as in MIN6 mouse pancreatic beta cells was determined by Western analysis using anti-GLP-1 receptor antibody. **(B)** Mouse primary macrophages were transfected with 100 nM scrambled (non-targeting) or GLP-1 receptor (GLP-1R) siRNAs for 2 days. Protein expression of GLP-1 receptor and actin was measured by Western analysis. **(C)** Insr+/+ or Insr-/- macrophages were treated with AcLDL and compound 58035 with or without exendin-4 (100 nM) or forskolin (10 uM) for indicated times. CHOP mRNA expression was monitored by real time QPCR. QPCR was performed in triplicate. n=3.



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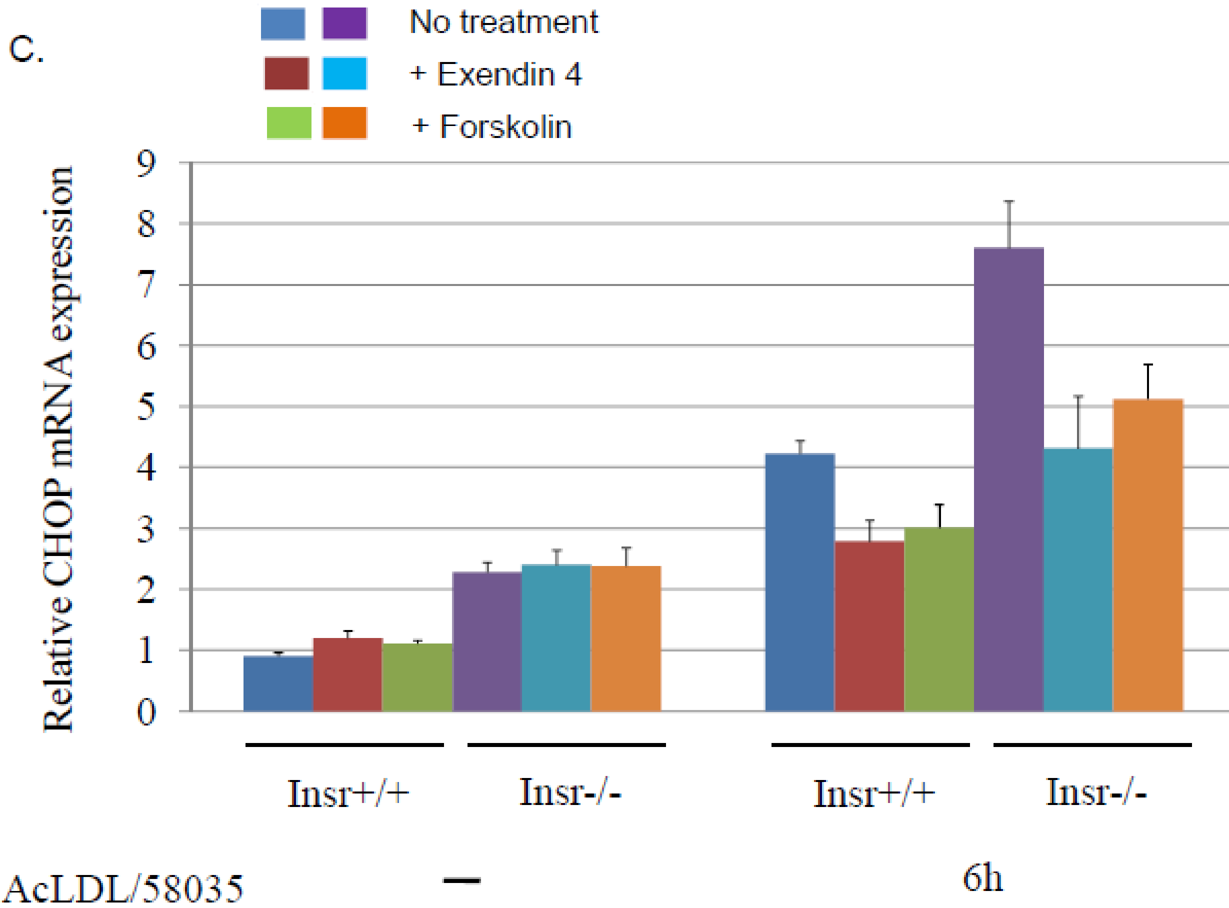

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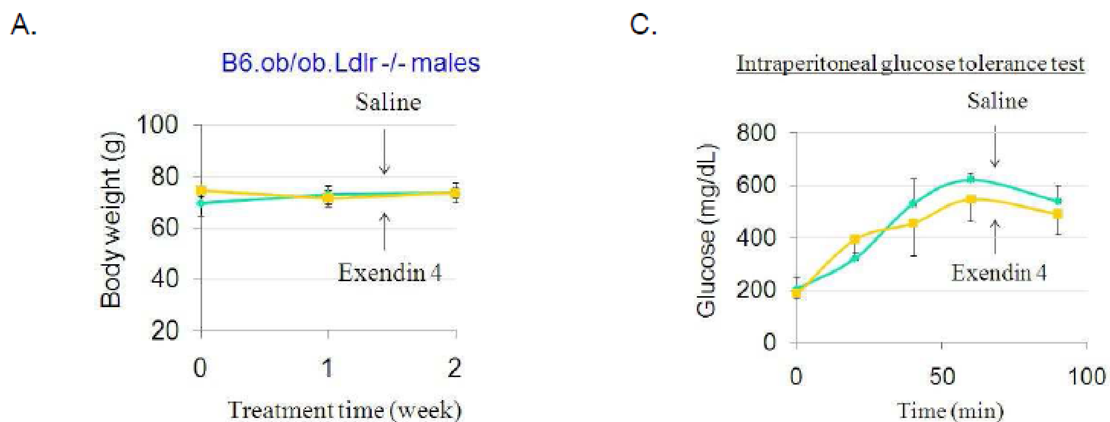
Supplementary Figure 4. Characterization of Ldlr-/- and ob/ob;Ldlr-/- mice treated with exenatide or saline. **(A)** Body weight of mice during the period of two-week treatment. Mice were fed Western-type diet for 3 months then received either PBS or exendin 4 (20 ng/g body weight) for two weeks under pair-feeding condition. n=4 for each ob/ob;Ldlr-/- group. **(B)** Plasma metabolic characteristics of ob/ob;Ldlr-/- mice with PBS or exendin 4 treatment described in (A). Metabolic profiles were monitored with plasma from mice fasted for overnight. **(C)** Glucose tolerance test with mice described in (A). Blood samples were obtained at indicated times after intraperitoneal injection of 2 g/kg body weight dextrose after overnight fasting. Blood glucose was determined using a Accu-Chek glucose monitor. **(D)** Primary macrophages isolated from Western-type diet-fed ob/ob;Ldlr-/- mice receiving PBS or exendin-4 in vivo were used for the analysis of SERCA2 by Western analysis (Left) or of Xbp1 mRNA splicing by real time QPCR (Right). *, P<0.05 for mice with in vivo treatment of PBS vs. exendin-4. n=3. **(E)** (Left) ConA-elicited peritoneal wild-type (WT) macrophages were treated with or without inhibitors of PI3K (LY294002, 10uM) or MEK (U0126, 10 uM). Protein lysate of macrophages treated with thapsigargin (Thap, 5 uM) was used as positive controls. The levels of indicated proteins were determined by Western analysis. (Right) Primary macrophages isolated from Western-type diet-fed ob/ob;Ldlr-/- and Ldlr-/- mice receiving PBS or exendin-4 in vivo were used for the analysis of ATF-3 and P-PERK by Western analysis. **(F and G)** Atherosclerotic aortic sections of ob/ob;Ldlr-/- and Ldlr-/- mice treated with PBS or exendin-4 were probed with antibody against ATF-3 or P-PERK, or control antibody followed by appropriate Alexa fluor-conjugated secondary antibody. Representative images of ATF-3 or P-PERK (green) overlaid with Hoechst-stained nuclei (blue) are shown. **(H)** Double immunofluorescence staining using antibodies against UPR markers ATF-3 or active caspase 3 and macrophage marker Mac-3 in atherosclerotic lesions of Insr-/-.Ldlr-/- mice with in vivo treatment of PBS or exendin-4. The data of ATF-3 or caspase 3 positive macrophages are expressed as % of total macrophages in the same lesion areas. *, P<0.05 for exendin-4 vs. saline-treated Insr-/-.Ldlr-/- mice. n=3.



B.

Treatment	ob/ob.Ldlr-/- PBS	Exendin 4
TG (mg/dl)	1500 ± 229	1295 ± 364
Cholesterol (mg/dl)	1738 ± 322	1519 ± 104

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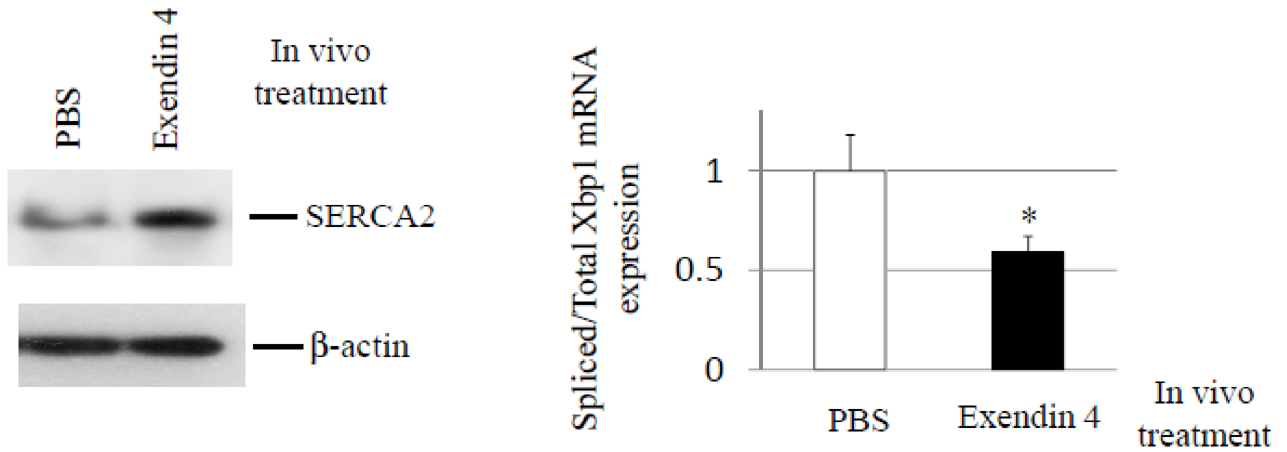

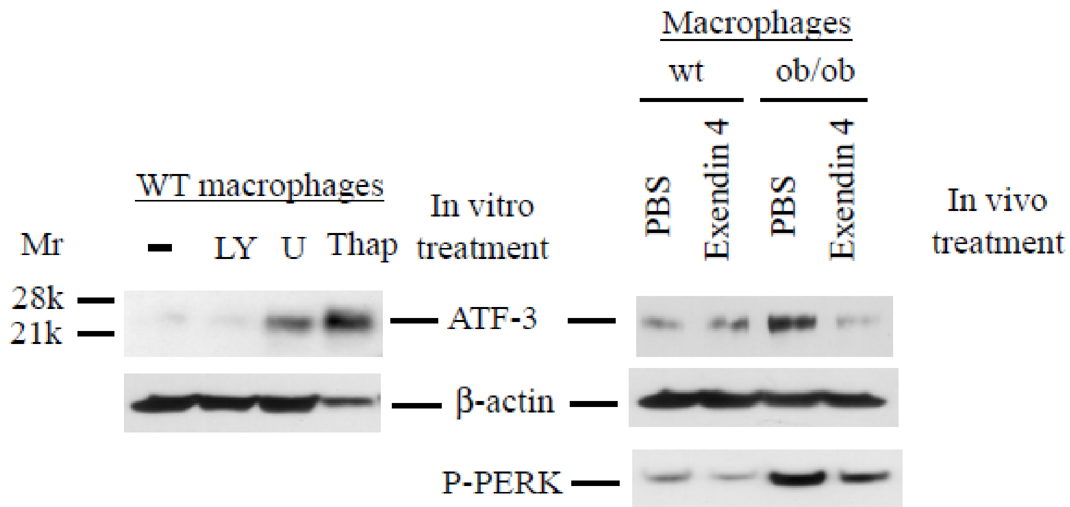

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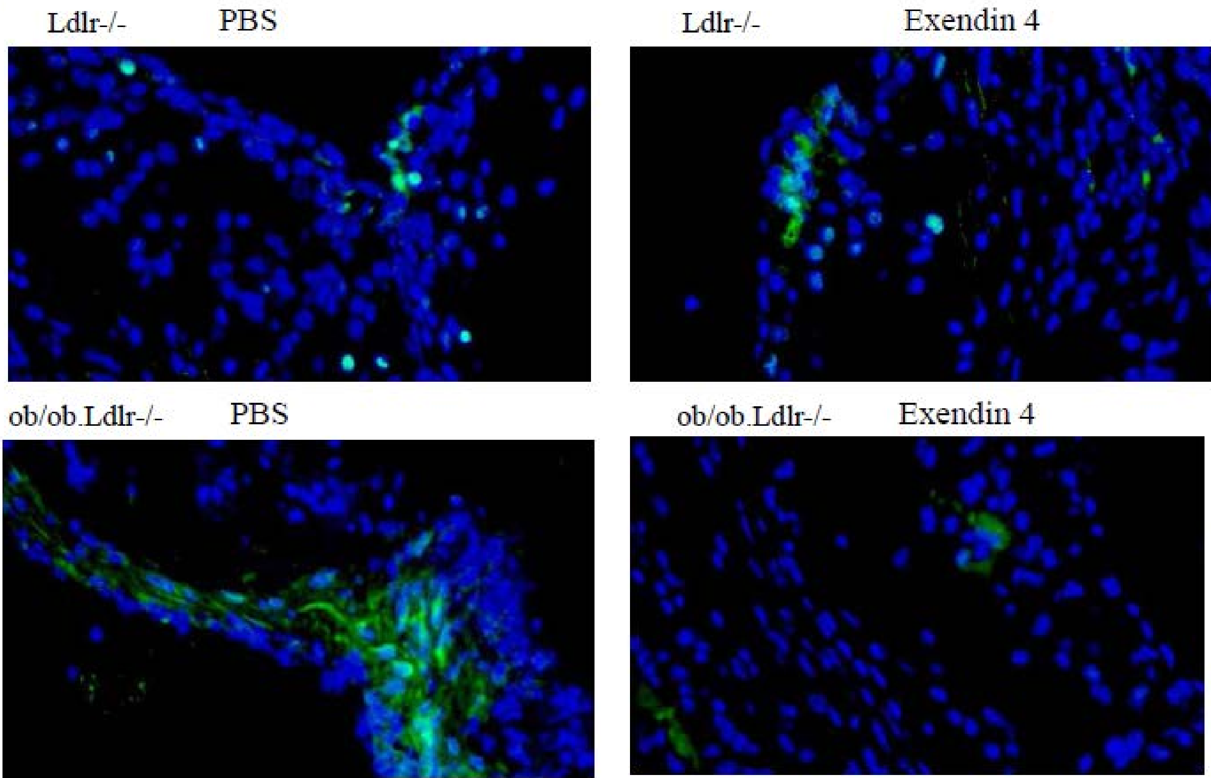

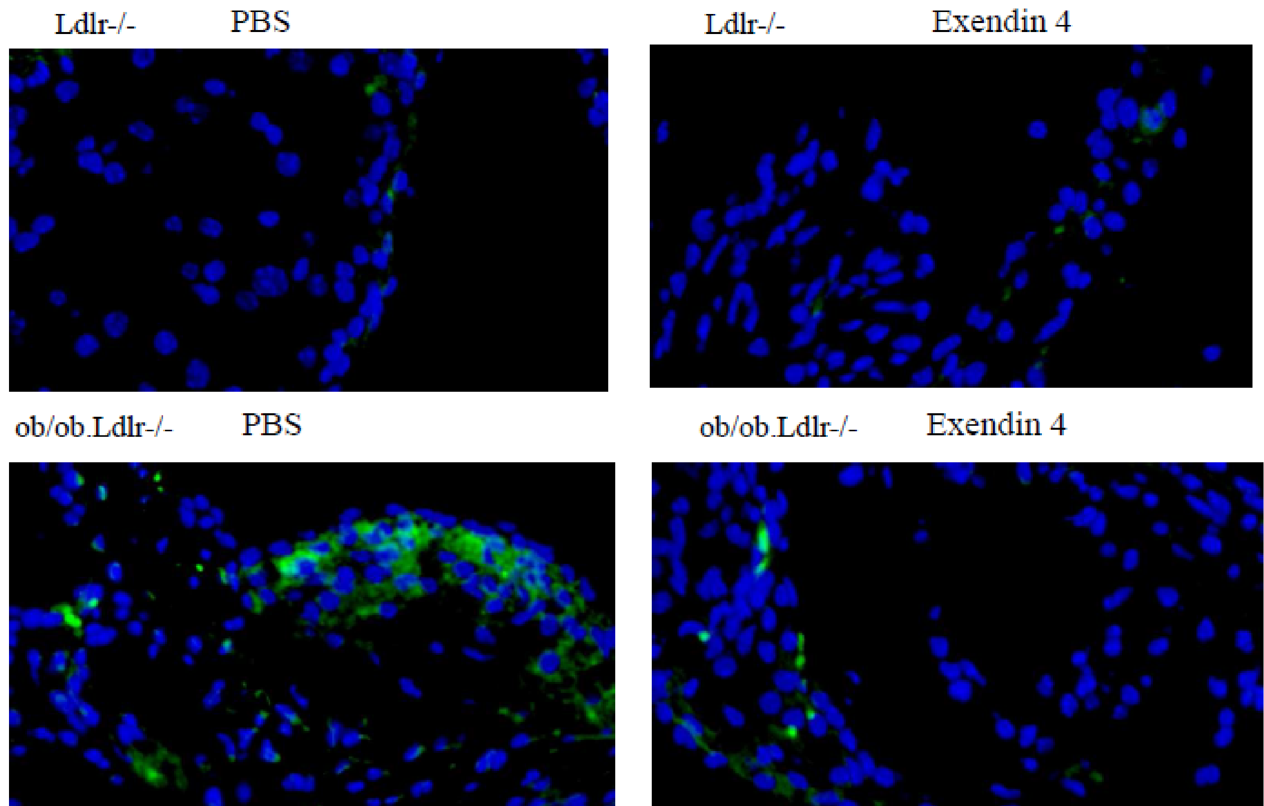

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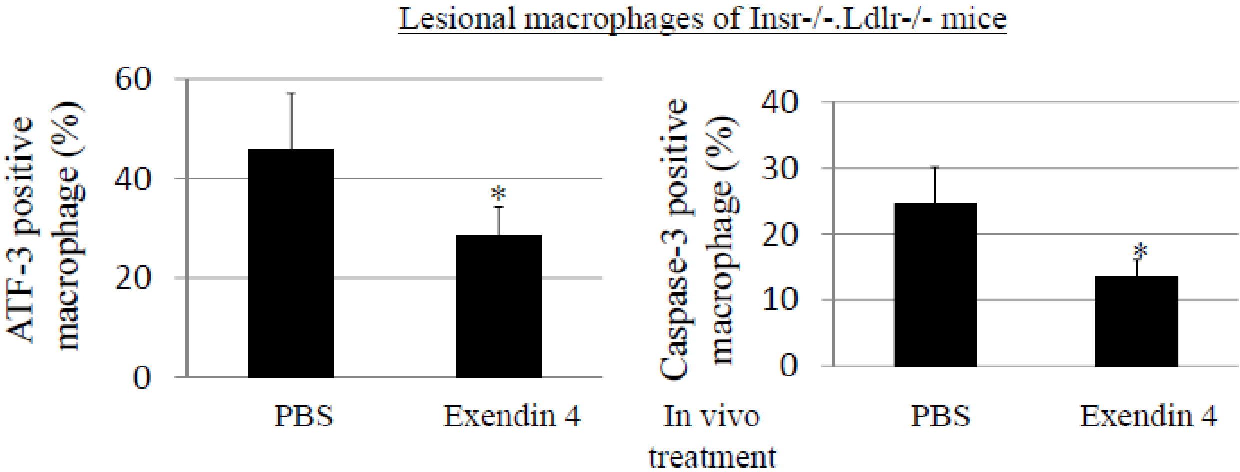

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